Metal-Free Hydrophosphorylation of C-C Unsaturated Bonds

著者	Huang Tianzeng
year	2018
その他のタイトル	金属を用いない炭素 : 炭素不飽和結合のヒドロホスホリル化に関する研究
学位授与大学	筑波大学 (University of Tsukuba)
学位授与年度	2018
報告番号	12102甲第8807号
URL	http://hdl.handle.net/2241/00153892

氏　　名	Huang Tianzeng
学 位 の 種 類	博 士 (理学)
学 位 記 番 号	博 甲 第　8807　号
学位授与年月日	平成 30年 9月 25日
学位授与の要件	学位規則第4条第1項該当
審 査 研 究 科	数理物質科学研究科
学 位 論 文 題 目	

Metal-Free Hydrophosphorylation of C-C Unsaturated Bonds
（金属を用いない炭素―炭素不飽和結合のヒドロホスホリル化に関する研究）

主	査	筑波大学教授 （連携大学院）	博士(工学) 韓 立彪
副	査	筑波大学教授	工学博士　鍋島 達弥
副	査	筑波大学教授	理学博士　市川 淳士
副	査	筑波大学教授	工学博士　小島 隆彦

論　文　の　要　旨

Mr. Tianzeng Huang's thesis described his achievements gained in studies on the development of new metal-free synthetic methods for organophosphorus compounds. Organophosphorus compound plays an important role in agricultural, pharmaceutical, organic synthesis, catalysts and materials chemistry. In this regard, a large number of these compounds have been prepared. However, only a limited number of synthetic methods have been developed. This is practically true for C-P bonding formation reactions. For example, the two widely employed classical methods for C-P bonding formation are the nucleophilic substitution reaction of a toxic halophosphorus compound with an organolithium or a Grignard reagent, and the Michaelis-Arbuzov reaction using a phosphite and an aliphatic halide, respectively. Tons of organophosphoryl compounds are prepared every year by these methods. However, these traditional methods suffer from drawbacks, such as low atomic efficiency and poor selectivity. The addition of a P(O)-H bond to carbon-carbon unsaturated bonds is one of the most direct and atomic-efficient way for the preparation of organophosphorus compounds. Recently, such additions catalyzed by a transition-metal catalyst are being extensively studied. For instance, the reaction of hydrogen phosphonate, $(RO)_2P(O)H$ with terminal alkynes forms the corresponding alkenylphosphonates in the presence of palladium or nickel catalysts. However, purification of the products was sometime difficult because of the strong coordination of the products to the metals. The contamination of a metal may significantly limits the applications of the products as pharmaceutical intermediates. To solve this drawback, a metal-free hydrophosphorylation (P(O)-H addition to C-C unsaturated bonds) are highly desirable. Compared to the successful transition metal promoted hydrophosphorylations, there are few reports of the metal free hydrophosphorylation of C-C unsaturated bonds.

In the thesis, the applicant studied the hydrophosphorylation of alkenes and alkynes with a variety of hydrogen phosphoryl compounds under metal-free conditions. Firstly, the applicant disclosed an efficient addition of hydrogen phosphoryl compounds to electron-deficient alkenes to obtained 1 to 1 adducts and 1 to 2 adducts using Me_3P as the catalyst. The primary advantage using Me_3P as a catalyst is the easy purification of the products because Me_3P can be easily removed from the products under *vacuum*. It was note that the formation of the 1 to 2 adducts has rarely been recognized so far in such additions of P(O)-H compounds to electron-deficient alkenes. The hydrophosphoylation of electron-deficient alkenes with P(O)-H compounds successfully generated selectivity 1 to 1 adducts in high yields when *t*-BuOH was used as the solvent. However, despite an extensive survey on the reaction conditions, such as solvent, other phosphine catalysts, additives and so on, the selective formation of 1 to 2 adducts has not been achieved yet. Therefore, the generation of 1 to 2 adducts was always accompanied by the formation of 1 to 1 adducts. Using Me_3P as catalyst, terminal alkenes with different electron-withdrawing groups successfully reacted with H-phosphonates, H-phosphinates and H-phosphine oxides in THF to give good to excellent total yields of the adducts. Based on control experiments, the applicant proposed a reaction mechanism that the combination of acrylonitrile with Me_3P can significantly deactivate the catalytic of Me_3P and the long-believed zwitterionic species by the addition of M_3P to acrylonitrile was not involved in the reaction.

Then, the applicant studied the photo-initiated and radical initiator-induced hydrophosphorylation of terminal alkynes with H-phosphine oxides and related compounds generating alkenylphosphine oxides. A mixture of $Ph_2P(O)H$ and 1-octyne was sealed in a Pyrex glass tube and irradiated by high-pressure Hg lamp for 4h to produced a mono-addition product as a *Z*- and *E*- isomer mixture and a side product by the double addition of $Ph_2P(O)H$ to 1-octyne. He found that the formation of the side product could be negligible by carrying out the reaction in a dilute solution and a suitable ratio of the two starting materials. A variety of aliphatic terminal alkynes was used as the substrates to produce the corresponding alkenylphosphoryl compounds in moderate to good yields under optimal reaction conditions. The conjugated alkynes and internal alkynes hardly produced the adducts, and most of the starting materials remained unreacted. He found that the reactivity of P(O)-H compounds roughly follows a decreasing order of H-phosphine oxide > H-phosphinate > H-phosphonate. Ph_2PH could also be used as the substrate to produce the corresponding alkenylphosphines in good yields. The *Z*- and *E*-isomer configuration of the synthesized compounds was assigned on the basis of ^{1}H-NMR spectra. The coupling constants of the alkenyl protons (J_{HH}) as well as that of J_{PH} allow the assignments of the *Z* and *E* isomers. He proposed a possible mechanism for this photo-induced hydrophosphorylation of terminal alkynes. The ratio of the *Z*- and *E*-isomers was determined by the stability and reactivity of the alkenyl radicals which exists in an equilibrium of *trans* and *cis* forms. The steric hindrance of the substituent of alkynes and phosphoryl compounds can efficiently affect the ratio of *Z*- and *E*- adducts. It was assumed that since silyl and OH groups may interact with the phosphoryl group to stabilize the *cis*- form radical, which consequently generated the *Z*-adducts as the major isomer form these bulky alkynes. As to the radical initiators, AIBN (Azobisisobutyronitrile), V-70 [2,2'-azobis(4-methoxy-2,4-dimethylvaleronitrile)] and V-601 [dimethyl 2,2'-azobis(isobutyrate)] were also effective in this hydrophosphoryl reaction, and good yields of the mono addition products with high *Z*/*E* selectively were obtained.

Finally, the applicant studied the application of phosphoryl compounds. He found that when diethyl

benzylphosphonate was mixed with 1.5 equiv. sodium *tert*-butoxide under dioxygen atmosphere in anhydrous DMF at room temperature, an almost quantitative yield of *trans*-stilbene was obtained. This reaction is a very convenient way for the synthesis of symmetrical stilbenes since the products are readily isolated by simply washing away the water-soluble phosphonate salts with water. Having established the optimal reaction conditions, the reaction was carried out using benzylic phosphonate bearing variety of substituents as substrates. Good to excellent yields of symmetrical *trans*-stilbene derivatives were obtained. Notably, in all cases, the reaction was highly selective for the formation of the *trans*-stilbene derivatives, and *cis*-stilbene derivatives were not detected from any of the examples as confirmed by GC and ^{1}H-NMR spectroscopies. A possible oxidative dephosphorylation coupling reaction mechanism was proposed via a peroxide intermediate since such a peroxide intermediate was confirmed by the isolation of (1-hydroperoxybutyl) diphenylphosphine oxide. In addition, the corresponding ketones were obtained in high yield from *α*-substituted benzyl phosphonates.

審　　査　　の　　要　　旨

〔批評〕

The applicant described three new reactions in his thesis, that is, (a) trimethylphospine-catalyzed additions of P(O)H compounds to electron deficient alkenes, (b) radical additions of P(O)H compounds to alkynes under light or initiated by a radical initiator, and (c) oxidative dephosphorylation of benzylphosphoryl compounds generating *trans*-stilbenes. The applicant cited the backgrounds of the study correctly, conducted the researches logically, and analyzed the results reliably, as evidenced by his three papers published in renowned international journals.

〔最終試験結果〕

The final examination committee conducted a meeting as a final examination on August 13, 2018. The applicant provided an overview of dissertation, addressed questions and comments raised during Q&A session. All of the committee members reached a final decision that the applicant has passed the final examination.

〔結論〕

Based on the results of the above-mentioned dissertation defense and final examination, the final examination committee approved that the applicant is qualified to be awarded Doctor of Philosophy in Science.